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Title: Nonbullous cutaneous pemphigoid: a systematic review

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ABSTRACT

Background: Cutaneous pemphigoid (bullous pemphigoid) is an autoimmune bullous disease that typically presents with tense bullae and severe pruritus. However, bullae may be lacking, a subtype termed nonbullous cutaneous pemphigoid.

Objective: To summarize the reported characteristics of nonbullous cutaneous pemphigoid.

Methods: The EMBASE and MEDLINE databases were searched using 'nonbullous cutaneous pemphigoid' and various synonyms. Case reports and series describing nonbullous cutaneous pemphigoid were included.

Results: The search identified 133 articles. After selection 39 articles were included, presenting 132 cases. Erythematous, urticarial plaques (52.3%) and papules/nodules (20.5%) were the most reported clinical features. The mean age at presentation was 74.9 years. Histopathology was commonly nonspecific. Linear depositions of IgG/C3 along the basement membrane zone were found by direct immunofluorescence microscopy in 93.2%. Indirect immunofluorescence on salt split skin was positive in 90.2%. The mean diagnostic delay was 22.6 months. The minority of patients (9.8%) developed bullae during the reported follow-up.

Limitations: Results are mainly based on case reports/small case series.

Conclusion: Nonbullous cutaneous pemphigoid is an underdiagnosed variant of pemphigoid that most often does not evolve to bullous lesions, and mimics other pruritic skin diseases. Greater awareness among physicians is needed to avoid delay in diagnosis.

INTRODUCTION

Cutaneous pemphigoid, also known as bullous pemphigoid (BP), is the most common autoimmune bullous disease affecting the skin and mucous membranes, with autoantibodies directed against the 180 kDa BP antigen (BP180) and the 230 kDa BP antigen (BP230) located in the basement membrane zone (BMZ).[1] The disease commonly affects older patients and is associated with an increased risk of mortality, as well as a significant decline in quality of life and psychological well-being.[2-6]

The clinical phenotype of cutaneous pemphigoid is polymorphic. The typical presentation consists of tense blisters that arise on erythematous, urticarial plaques, and is accompanied by severe pruritus.[1,3] Prior to blister formation pruritus can occur as a prodrome, with or without primary skin manifestations.[7] In contrast to the typical bullous presentation, various atypical variants of cutaneous pemphigoid have been reported with terms such as papular pemphigoid, pemphigoid nodularis, pemphigoid vegetans, erythrodermic pemphigoid, pruritic nonbullous pemphigoid and erythema multiforme-like pemphigoid.[8-11] The nonbullous variant of cutaneous pemphigoid presents with pruritus and various nonbullous findings on the skin, such as erythematous patches, urticarial plaques, papules, nodules, excoriations, eczema, and erythroderma. Moreover, this variant can even present without primary skin lesions, called 'pruritus on primary, non-diseased, non-inflamed skin' according to the International Clinical Classification of Itch.[11,12] Previous articles have emphasized the need for uniform terminology and discussed the urge for renaming *bullous pemphigoid*, since the use of the adjective '*bullous*' is redundant considering that '*pemphigoid*' means 'resembling pemphigus' and pemphigus is Greek for *'blister'*.[8,13-15] Borradori and Joly proposed the term '*cutaneous pemphigoid*'.[13] To emphasize the lack of bullae in the nonbullous disease variant, we proposed to add the adjective *nonbullous.*[14] Hence, the terminology used in this article.

Cohort studies show that at least 20% of all pemphigoid patients do not have blisters at the time of diagnosis.[3,15] Thus, nonbullous cutaneous pemphigoid is not that uncommon or atypical as may be assumed.[16] The bullous and nonbullous cutaneous pemphigoid phenotypes are immunologically indistinguishable. The diagnosis is usually based on the combination of clinical presentation, histopathological findings, direct immunofluorescence

(DIF) microscopy, and immunoserology.[15] One of the main obstacles currently is the lack of consensus on the minimal diagnostic criteria of cutaneous pemphigoid.[8,13,14,16,17] The absence of blistering in nonbullous cutaneous pemphigoid can make the recognition of this disease difficult for clinicians and may result in a delay of diagnosis.[18,19]

The aim of our study is to characterize and define nonbullous cutaneous pemphigoid by systematic review, which has not been performed before. Our study lists reported clinical presentations, histopathological findings, laboratory findings, and prognosis regarding patients with nonbullous cutaneous pemphigoid.

MATERIALS AND METHODS

Search strategy

The literature search for this review was conducted in the EMBASE and MEDLINE databases on the 4th of November 2016. Various terms and synonyms for *'nonbullous cutaneous pemphigoid'* were used (supplement 1). There were no limitations on article type. After the selection procedure the references of all included articles were checked for missing articles.

Selection of articles

Language was limited to Dutch, German or English. Independent screening of the titles and abstracts was carried out by AL and JM. Discrepancies between the researchers were resolved through discussion. All articles reporting on one or multiple cases of nonbullous cutaneous pemphigoid were included. Nonbullous cutaneous pemphigoid was defined as all symptomatic cases with a nonbullous phenotype, that lacked a previous history of bullae, and fulfill the following diagnostic criteria of cutaneous pemphigoid: a positive DIF with linear IgG and/or C3c along the BMZ and/or positive indirect immunofluorescence (IIF), in combination with compatible clinical presentation, histopathological findings, or other immunoserological tests. If the full text was not available online it was ordered at the national library. Poster abstracts were only included if sufficient individual patient data was presented.

Data collection

The following variables were gathered: age at diagnosis, gender, duration of symptoms before the diagnosis was made, clinical presentation, results of diagnostic tests, histopathological findings, total follow-up time and whether blisters developed during follow-up. Statistical analyses were done in IBM SPSS statistics 23.

RESULTS

Systematic search results

A total of 39 articles presenting a total of 132 cases of nonbullous cutaneous pemphigoid were identified (supplement 2). Figure 1 displays the selection procedure. The first case of nonbullous cutaneous pemphigoid was reported in 1983 by Barker et al.[20] The largest case series was from Lamb et al.[21], who described the clinical presentation of 53 patients diagnosed with 'prodromal bullous pemphigoid'. This large case series did not present individual patient characteristics concerning age, gender, duration of symptoms, histopathological findings and total duration of follow-up. However, we were able to include the reported clinical presentation and the number of cases that developed blisters during follow-up.

Clinical presentation

Table 1 shows the demographics of the reported patients with nonbullous cutaneous pemphigoid. The mean age at presentation was 74.9 years. The reported efflorescences and configurations of skin lesions seen at dermatological examination are displayed in table 2. Table 3 presents the location of skin lesions, reported in 64 of the 132 cases.

Histopathology

The histopathological findings were described in 53 individual cases. A perivascular infiltrate was seen most frequently (n=32; 60.4%), which is a non-specific finding. Additionally, non-specific findings not further specified were reported in 14 cases (26.4%). Eosinophils were present in the biopsies of 25 cases (47.2%) and neutrophils in 7 cases (13.2%). Spongiosis without eosinophils was reported in 10 cases (18.9%), while eosinophilic spongiosis was seen in 4 patients (7.5%). The presence of dermal edema was reported in 8 cases (15.1%). The presence of a microscopic subepidermal split was reported in 8 patients (15.1%).

Laboratory findings

Table 4 shows the reported laboratory findings of patients with nonbullous cutaneous pemphigoid. In all cases DIF microscopy was performed. In cases with a negative DIF result, the diagnosis was based on positive IIF with additional serological tests that specified the

targeted antigen. IIF was the most commonly performed immunoserological test (55 cases). The substrate used in IIF was not specified in 15 cases. In the other cases monkey esophagus (n=27) or human skin (n=13) were used as substrate. The BP230 ELISA was the least performed immunoserological test (n=19). Additionally in four cases immunoprecipitation was used to identify antigens, resulting in a positive reaction to both BP180 and BP230 in one case and only a positive reaction to BP230 in three cases. Eosinophilia in peripheral blood was reported in 13 of 15 cases (86.7%).

DISCUSSION

This systematic review summarizes the reported characteristics of nonbullous cutaneous pemphigoid. The most frequently reported skin efflorescences were erythematous, urticarial plaques (52.3%). Pruritus was reported in 100% of the cases. Overall, the duration between the start of symptoms and the correct diagnosis was very long (mean 22.6 months). Only 13 patients (9.8%) developed bullae during the reported follow-up, thus were actually prodromal to the bullous phase of cutaneous pemphigoid. However, in the majority of the cases (90.2%) bullae never occurred. The findings of this review show that although the clinical presentation of nonbullous cutaneous pemphigoid is various, pruritus at high age may be a clinical clue.

Our study identified several similarities in clinical characteristics of nonbullous and bullous cutaneous pemphigoid. Both present at older age (mean 74.9 versus 77.2 – 82.6 years).[4-6] Furthermore, in both variants lesions are most frequently located on the trunk and extremities.[18,22] Most of the skin efflorescences reported in nonbullous cutaneous pemphigoid cases can also be found in patients with cutaneous pemphigoid with bullae.[1,15] On the other hand, mucosal involvement was rarely reported in nonbullous cutaneous pemphigoid, while reported in 10-30% of patients with cutaneous pemphigoid.[3,15,22] In 14 cases the configurations of the skin lesions were reported to be annular, gyrate, figurate or herpetiform.[21,23-30] Two of these patients presented with targetoid lesions.[21,25] We also found three case reports that were possibly drug induced due to nifedipine, lisinopril and the combination of allopurinol plus colchicine.[25,31,32] Nifedipine and lisinopril were previously associated with cutaneous pemphigoid, however it is not shown that these drugs actually cause a higher risk to develop cutaneous pemphigoid.[33,34] Studies did show that the use of spironolactone and neuroleptics are independent risk factors for the development of cutaneous pemphigoid.[35,36]

The reported histopathological findings in nonbullous cutaneous pemphigoid differ from cutaneous pemphigoid with typical bullae in several aspects. Histopathological findings were commonly nonspecific in nonbullous cutaneous pemphigoid and resembled eczema or prurigo nodularis. While cutaneous pemphigoid with bullae is usually characterized by the presence of eosinophilic spongiosis (>50%) and a subepidermal split (± 80%), in the cases

with nonbullous cutaneous pemphigoid histopathological findings only described eosinophilic spongiosis in 7.5% and a subepidermal split in 15.1%.[1,37] These findings emphasize the need to always perform DIF microscopy and immunoserology in addition to histopathology in patients in which nonbullous cutaneous pemphigoid is suspected. In nonbullous cutaneous pemphigoid DIF microscopy was the most reported positive diagnostic test (positive in 93.2%) followed by IIF on salt-split skin (SSS) (90.2%). Both DIF microscopy and IIF on SSS have a high specificity (98% and 100% respectively).[38] Yet, the reported percentage of positive findings in DIF microscopy in nonbullous cutaneous pemphigoid might be an overestimation, since this test is regarded as the reference standard for diagnosis of pemphigoid and commonly the only performed immunopathological test.[39] Consequently the diagnosis of pemphigoid might be rejected when DIF microscopy is negative and immunoserological analysis might not have been performed.

The mean duration of symptoms of nonbullous cutaneous pemphigoid until the correct diagnosis of pemphigoid was 22.6 months. These results seem to be consistent with other research that also found long diagnostic delays in pemphigoid cases that lack bullae. Previously, we reported a mean delay in diagnosis of 33.6 months in 15 patients with nonbullous cutaneous pemphigoid.[14] The studies of Zhang et al. and Sun et al. reported misdiagnosis with eczema, nodular prurigo or other dermatologic diseases in all pemphigoid patients that initially presented without bullae, 181 and 24 patients respectively.[18,40] In both studies the correct diagnosis was made when bullae appeared, which was after a mean duration of 15.9 months and 20.75 months (range 1 month to 19 years). Although these studies only identified misdiagnosis in prodromal cutaneous pemphigoid patients, they also illustrate the importance of more awareness and better knowledge regarding the characteristics of nonbullous cutaneous pemphigoid. In contrast, Della Torre et al. did not find a significant difference in delay of diagnosis between patients with bullous (n=97) and nonbullous (n=20) cutaneous pemphigoid in their cohort.[3] Whether early recognition and immunosuppressive treatment of nonbullous cutaneous pemphigoid can prevent later blister development is unknown.

A much debated question is whether patients diagnosed with nonbullous cutaneous pemphigoid are prodromal or have a distinct pemphigoid variant.[10,21] The finding that the

majority of nonbullous cutaneous pemphigoid patients did not develop blisters during follow-up supports the hypothesis that nonbullous cutaneous pemphigoid is not a prodromal stage but merely a variant within the clinical spectrum of pemphigoid diseases. We can conclude that 'prodromal pemphigoid' is an incorrect term and that there is a need for consensus regarding the terminology to describe this disease variant. We strongly argue for insertion of the term nonbullous cutaneous pemphigoid in the EMTREE.

During our literature search we identified a number of other subepidermal autoimmune blistering diseases with nonbullous clinical presentations: nonbullous epidermolysis bullosa acquisita[41], nonbullous linear IgA dermatosis[42] and nonbullous pemphigoid gestationis[43]. Furthermore we came across reports of cutaneous pemphigoid patients that first presented with bullae and later experienced a nonbullous flare-up of the disease.[44-49] These cases strengthen the idea that nonbullous cutaneous pemphigoid should be seen as a disease variant within the spectrum of pemphigoid diseases. Previous publications reported a higher prevalence of BP-specific autoantibodies in older dermatology patients (>75 years) without blisters, healthy blood donors, and elderly individuals with pruritus.[50-52] How these patients fit the pemphigoid spectrum has not been clarified.

Our systematic review provides insight on reported literature on nonbullous cutaneous pemphigoid so far. A limitation of this review is that the results are mainly based on single case reports and small case series. Consequently missing values were present in the summarized data. Moreover, in some publications the clinical picture was described very briefly. A second limitation of this review is the risk of reporting bias, since cases with unusual atypical presentations are more likely to be reported in the literature. Furthermore, the finding that the majority (90.2%) of nonbullous cutaneous pemphigoid patients did not develop blisters during the reported follow-up (mean 19.8 months;range 0-72) might be slightly biased by selection, since we excluded cases of cutaneous pemphigoid that were diagnosed after bullae appeared, even though authors retrospectively described pruritic symptoms prior to blistering. However, it is uncertain whether these symptoms prior to diagnosis were caused by pemphigoid, or by other pruritic dermatoses, such as prurigo nodularis or eczema. This study therefore highlights the importance of larger observational studies with longer follow-up for a better representation of nonbullous cutaneous pemphigoid

Another interesting focus for future research is why patients with nonbullous cutaneous pemphigoid do not develop bullae. Several factors have been suggested to influence blister formation, such as autoantibody titers,[53] the antigens or epitopes targeted by autoantibodies,[22,54] complement involvement,[55,56] and eosinophils.[57] More knowledge of the underlying pathophysiology of this subtype of pemphigoid might lead to more awareness and less delay in diagnosis of nonbullous cutaneous pemphigoid.

In conclusion, our review showed that the reported clinical presentation of nonbullous cutaneous pemphigoid can be heterogeneous. The reported long duration of symptoms until correct diagnosis (mean 22.6 months) illustrates that nonbullous cutaneous pemphigoid can be difficult to recognize for clinicians. Pruritus in elderly is a common denominator in patients with nonbullous cutaneous pemphigoid and in our opinion the most important clue for recognition. Clinicians should therefore perform DIF on a skin biopsy and immunoserological analysis on a blood sample in elderly with unexplained or refractory chronic pruritus and erythematous, urticarial papules and plaques. Further study is needed to evaluate the prevalence of nonbullous cutaneous pemphigoid.

ABBREVIATION LIST

BP	bullous pemphigoid
BP180	180 kDa BP antigen
BP230	230 kDa BP antigen
BMZ	basement membrane zone
DIF	direct immunofluorescence
IIF	indirect immunofluorescence
SSS	salt-split skin

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LEGENDS TO FIGURES

Figure 1 Study selection flow diagram

TABLES

Table 1

Table 1. Demographics of the reported cases of nonbullous cutaneous pemphigoid

Demographic outcome measurements			Reported in no. of cases
Mean age at presentation, in years	74.9	SD 11.8; range 39-95	78
Male cases, proportion	33 (42.3%)		78
Cases experiencing pruritus, proportion	77 (100%)		77
Cases with reported mucosal lesions, proportion	1* (7.1%)		14
Mean duration of symptoms before diagnosis, in months	22.6	SD 39.1; range 0-240	50
Cases with blister development after diagnosis, proportion	13 (9.8%)		132
- Mean duration of symptoms until blisters occurred, in months	15.9	SD 8.4; range 7.5-27	5
- Mean duration from diagnosis till blisters occurred, in months	9.6	SD 8.6; range 1-21	7
Mean total follow-up, in months	19.6	SD 18.6; range 0-72	46

SD, standard deviation; * Ulceration in the mouth that healed without scarring, other mucosal areas were spared [32]

Table 2

Table 2. Skin findings and configurations reported in cases of nonbullous cutaneous pemphigoid

Skin findings reported	No. of cases (%)
Erythematous, urticarial papules and plaques	69 (52.3%)
Papules/nodules	27 (20.5%)
Eczematous lesions	16 (12.1%)
No primary lesions reported¶	6 (4.5%)
Dermatitis herpetiformis-like lesions	5 (3.8%)
Ulcerations	3 (2.3%)
Erythroderma	3 (2.3%)
Other:	
Scarring alopecia	1 (0.8%)
Vegetations	1 (0.8%)
Solitary macule	1 (0.8%)
Excoriations	30 (22.7%)
Configuration reported	
Annular configuration*	8 (6.1%)
Figurated configuration	2 (1.5%)
Gyrated configuration	1 (0.8%)

The clinical presentation was reported in all 132 cases.
¶ all 6 cases presented with secondary lesions in the form of excoriations
** two cases presented with erythema mulitformis-like lesions*

Table 3

Table 3. Reported localization of skin lesions in nonbullous cutaneous pemphigoid

Localization reported	No. of cases (%)
Extremities	43 (67.2%)
Trunk	42 (65.6%)
Generalized	14 (21.9%)
Head and/or neck	7 (10.9%)
Scalp	6 (9.4%)
Hands and/or feet	5 (7.8%)

The localization of the lesions was reported in 64 cases

500
501

502 **Table 4**

Table 4. Reported laboratory findings

	No. of cases with positive test results (%)	Reported in no. cases
DIF microscopy, linear IgG and/or C3c depositions along the BMZ	123 (93.2%)	132
IIF* IgG	42 (76.4%)	55
IIF on salt split skin, IgG, epidermal binding	46 (90.2%)	51
Nc16a ELISA, IgG	15 (57.7%)	26
BP230 ELISA, IgG	10 (52.6%)	19
Immunoblot BP180, IgG	11 (32.4%)	34
Immunoblot BP230, IgG	20 (55.6%)	36

503 *DIF,* direct immunofluorescence; IgG, immunoglobulin G; BMZ, basement membrane zone; IIF, indirect
504 immunofluorescence; Nc16a, non-collagen 16a; ELISA, enzyme linked immunosorbent assay.
505 ** different substrates were used by different authors.*
506
507

SUPPLEMENTARY MATERIAL

Supplement 1

Keywords used in the systematic search (performed in EMBASE & MEDLINE)

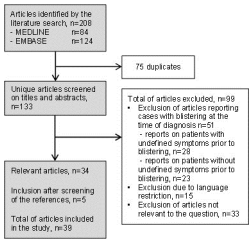
('non*bullous' AND 'pemphigoid') OR 'non*bullous pemphigoid' OR non*bullous bullous pemphigoid' OR 'non*bullous BP' OR 'pruritic pemphigoid' OR 'pruritic non*bullous pemphigoid' OR 'pemphigoid nodularis' OR 'nodular pemphigoid' OR 'prurigo nodularis-like pemphigoid' OR 'papular pemphigoid' OR 'prodromal BP' OR 'prodromal bullous pemphigoid' OR 'prodromal pemphigoid' OR 'prodrome of bullous pemphigoid' OR 'non bullous variant' NEAR/10 'pemphigoid' OR 'nonbullous variant' NEAR/10 'pemphigoid' OR 'bullous pemphigoid mimicking' OR '-like bullous pemphigoid' OR 'erythrodermic bullous pemphigoid' OR ('bullous pemphigoid' AND 'without blister*') OR ('bullous pemphigoid'/exp AND 'without blister*') OR ('bullous pemphigoid' AND 'without bullae') OR ('bullous pemphigoid' AND 'without bullous lesions')

Supplement 2

List of all included articles presenting cases of nonbullous cutaneous pemphigoid

First author	Publication year
Barker et al.[20]	1983
Bingham et al.[58]	1984
Amato et al.[24]	1988
Borradori et al.[59]	1990
Wolf et al.[60]	1992
Ross et al.[49]	1992
Strohal et al.[10]	1993
Bourke et al.[45]	1994
Wever et al.[61]	1995
Jeong et al.[62]	1995
Cliff et al.[63]	1996
Kawahara et al.[53]	1997
Alonso-Llamazares et al.[64]	1998
Alonso-Llamazares et al.[65]	1998
Scrivener et al.[66]	1999
Ameen et al.[32]	2000
Schmidt et al.[67]	2002
Powell et al.[68]	2002
Goel et al.[69]	2003
Mechtel et al.[70]	2003

Tashiro et al.[30]	2005
von Felbert et al.[71]	2005
Lamb et al.[21]	2006
Yesudian et al.[72]	2009
Matsudate et al.[73]	2009
Axelrod et al.[25]	2010
Safa et al.[74]	2010
McCourt et al.[75]	2010
Geiss Steiner et al.[76]	2010
Lehman et al.[77]	2011
Patel et al.[29]	2012
Bakker et al.[11]	2013
Balakirski et al.[78]	2014
Liu et al.[31]	2014
Kabuto et al.[27]	2015
Altman et al.[23]	2015
Park et al.[28]	2015
Huet et al.[79]	2016
Ise et al.[26]	2016



Capsule summary

- What is already known on this topic.
  Cutaneous pemphigoid can present without typical bullae and consequently diagnosis can be delayed.

- What this article adds to our knowledge.
  The most frequently reported clinical features in these patients are pruritic, erythematous, urticarial papules and plaques.
- How this information impacts clinical practice and/or changes patient care.
  Clinicians should consider nonbullous cutaneous pemphigoid in older patients with refractory pruritus.